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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, DC 20460

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MAY 24 1989

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Peer Review of Ethofenprox

TO: Adam Heyward
Product Manager, Team 15
Registration Division (H7505c)

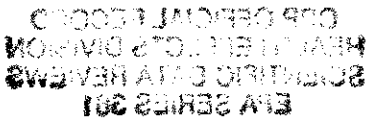
FROM: William F. Sette, Ph.D. William F. Sette 4/12/90
Executive Secretary, Peer Review Committee
Science Analysis and Coordination Branch
Health Effects Division (H7509c)

The Health Effects Division Peer Review Committee met on May 31, 1989 to discuss and evaluate the weight of the evidence on Ethofenprox with special reference to its carcinogenic potential. We concluded that the weight of evidence should be classified as Group C, Possible Human Carcinogen, and recommended that a quantitative risk assessment should be performed on the rat thyroid tumors.

A. Individuals in Attendance

1. Peer Review Committee (Signature indicates concurrence with the peer review unless otherwise stated.)

Penelope A. Fenner-Crisp
William L. Burnam
Reto Engler
Kerry Dearfield
George Ghali
Richard Hill
Richard Levy
John A. Quest
Esther Rinde
William Sette



2. Scientific Reviewers (People responsible for presentation of data; signature indicates technical accuracy of panel report.)

Sidney Stolzenberg — 4-13-90

Mike Ioannou — 4-13-90

Bernice Fisher — 4-18-90

3. Peer Review Members in Absentia (Those unable to attend the discussions; signature indicates concurrence with overall conclusions of the Committee.)

Marcia Van Gemert

Karl Baetcke

Robert Beliles

Marion Copley

4. Other Attendees Hugh Pettigrew

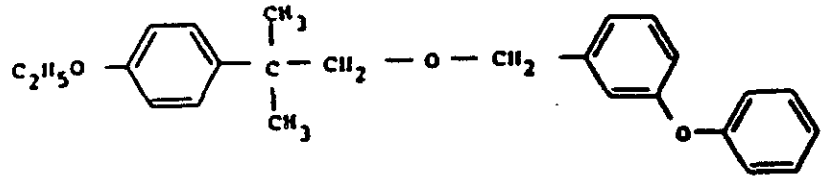
B. Material Received

We received a package from Dr. Stolzenberg composed of 6 parts and a 7th from Bernice Fisher:

A. General Information;
B. Summary of Neoplastic Findings and Overview of the Carcinogenicity Studies;
C. Statistical Analysis of the Rat Tumors; C.J. Nelson, 6/16/88
D. Summaries of Other Toxicity Studies;
E. Review of Carcinogenicity of Structural Analogues;
F. an Appendix of one-liners and the Data Evaluation Records of the Carcinogenicity Studies.
G. Statistical Analysis of the Mouse Tumors; B. Fisher, 5/24/89

C. Background Information

Structure of Ethofenprox



2-(4-Ethoxyphenyl)-2-methylpropyl-3-phenoxybenzylether

Ethofenprox is a new phenoxybenzylether insecticide considered a synthetic pyrethroid by the manufacturer proposed for indoor, household use. With aerosol or fogger use in kitchens, indirect contamination of foods may reasonably be expected.

Ethofenprox is Category IV for acute oral toxicity in both the rat and the dog.

There are 2 subchronic feeding studies.

In rats, significantly decreased body weights, enlarged livers, adrenals, and thyroids, decreased thymus weight, and liver histopathology were seen at 10,800 ppm and liver enzyme changes at 1800 ppm; the NOEL was 300 ppm (20 mg/kg). The doses tested were 50, 300, 1800, and 10,800 ppm.

In the mouse, 15,000 ppm caused liver and kidney histopathology and increased organ weights. The NOEL was 3,000 ppm (375 mg/kg). The doses tested were 50, 500, 3,000, and 15,000 ppm.

In a 90 day inhalation study in rats, organ weight increases and microscopic changes were seen at 0.2 g/m3(aerosol); the NOEL was 0.04 g/m3.

D. Evaluation of Carcinogenicity Evidence for Ethofenprox

1. "Ethofenprox (MTI-500) Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Rats". Huntingdon Research Center, England. Study No. MTC 59/85581. Final Report Date 12/15/87. EPA MRID No. 404497-07.

Ethofenprox was administered in the diets of Sprague-Dawley rats at levels of 0, 30, 100, 700, and 4900 ppm in the diet for 2 years.

There were no survival problems for either sex.
For females, there was a statistically significant increase in comparison to controls for thyroid follicular cell adenomas at 4900 ppm and a significant positive trend in this tumor type for both

sexes. There were no significant trends or pairwise comparisons for either sex in thyroid follicular carcinomas or thyroid parafollicular carcinomas. The incidence of thyroid follicular cell adenomas and carcinomas combined in the 4900 ppm group was statistically significantly increased compared to controls in both sexes and there were significant positive trends for these combined tumors for both sexes as well.

Historical control data were provided for thyroid tumors from studies conducted between 3/82 and 8/85. Combined thyroid follicular cell carcinomas and adenomas ranged from 3.6 to 16.7% in males, and from 0 to 6% in females. In the present study, the high dose percentages of these combined tumors were 16% for females and 24% for males, both outside the historical control ranges.

Other Effects

Other effects observed in this study were body weight decreases, liver changes, and thyroid changes.

They included:

Statistically significant decreases in body weight gain in both sexes(13.2% in males, 7.2% in females) at the high dose;
significantly ($p<0.05$) increased thyroid weights in high dose males at week 26 and mid and high dose males at week 107;
some cystic follicles in females (4/50 controls vs. 13/50 at 4900 ppm);increased follicle cell height in 5/10 females at 4900 ppm at 26 weeks;
decreased T3 levels in high dose females at week 25;
significantly increased liver weights in both sexes at 4900 ppm at 26, 52, and 107 weeks;
enlarged livers in both sexes at the high dose at 26 and 52 weeks and high dose males in the main study (at 2 years);
centrilobular hepatocyte enlargement in high dose males and females at terminal sacrifice (0 controls, 5/27 males, 8/26 females), with similar increases at 26, but not 52 weeks (9 males and 3 females);
focal areas of eosinophilic hepatocytes in mid and high dose males and high dose females; high dose females also showed vacuolated eosinophilic hepatocytes;
and hepatocyte necrosis/inflammation in high dose females (5/27 vs.0 in controls).

The high dose tested was considered adequate for carcinogenicity testing based on the results in males (e.g. body weight) and on the effects seen in both sexes in the 13 week study at 10,800 ppm. In the female, the level appeared to approach one that would have caused significant toxicity. Further, the Committee felt that the selection of 4900 ppm as a high dose based on the effects seen in 90 days at 10,800 ppm, which included liver histopathology and significant body weight changes, was reasonable.

TABLE V

INCIDENCE OF THYROID FOLLICULAR ADENOMAS AND ADENOCARCINOMAS IN RATS OF HISTORICAL CONTROLS

Study Code	R		S		T		U		V		W	
	D	T	D	T	D	T	D	T	D	T	D	T
Males; number examined	80	25	24	26	37	23	26	23	26	29	32	18
Follicular adenoma	3	1	2	2	2	6	3	3	1	1	1	2
Follicular adenocar.	2	1			0	2						
Percent (all tumors)	6.7		8.0		16.7		12.2		3.6		6.0	
Females; number examined	77	28	30	19	34	27	24	25	26	29	33	17
Follicular adenoma	1	0			1	0			0	1	0	3
Follicular adenocar.	0	2										
Percent (all tumors)	2.9		0.0		1.6		0.0		1.8		6.0	

D Died during the course of the study
T Killed at the termination of the study

TABLE 6. ETHOFENPROX - Male Rat Thyroid Follicular Tumor Rates and Cochran-Armitage Trend Test and Fisher's Exact Test Results

	DOSES				
	0	30	100	700	4900
Adenoma	6/58 (10)**	6/60 (10)	4/60 (7)	5/58 (9)	12/59 (20)a)
Carcinoma	0/25 (0)	0/27 (0)	1/25 (4)	3/29 (10)	2/27b) (7)
Combined	6/58 (10)**	6/60 (10)	5/60a) (8)	8/58 (14)	14/59a) (24)*

a) First adenoma occurred at 53 weeks in dose 4900 ppm.
b) First carcinoma occurred at 107 weeks in dose 4900 ppm.

TABLE 4. ETHOFENPROX - Female Rat Thyroid Follicular Tumor Rates and Cochran-Armitage Trend Test and Fisher's Exact Test Results

	DOSES				
	0	30	100	700	4900
Adenoma	0/59 (0)**	3/57 (5)	3/58a) (5)	0/60 (0)	8/58 (14)**
Carcinoma	0/27 (0)	0/20 (0)	0/22 (0)	2/22b) (9)	1/29 (3)
Combined	0/59 (0)**	3/57 (5)	3/58a) (5)	2/60 (3)	9/58 (16)**

a) First adenoma occurred at 53 weeks in dose 100 ppm.
b) First carcinoma occurred at 106 weeks in dose 700 ppm.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then $p<.05$ and if ** then $p<.01$.

2. "Ethofenprox (MTI-500) Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Mice". Huntingdon Research Center, England. Study No. MTC 58/85582. Final Report Date 1/6/86. EPA MRID No. 404497-09.

CD-1 mice were fed 0, 30, 100, 700, or 4900 ppm of Ethofenprox in their diet for 108 weeks.

For females, there were no survival differences and no significant increase in any tumors.

For males there were statistically significant increases in deaths at the 100 and 4900 ppm doses by pairwise comparison, and a significant increasing trend in mortality. Male mice had a significant dose related positive trend in renal cortical adenomas alone and combined carcinomas and adenomas. There were no significant pairwise comparisons. The observed incidence (1/58, 1.7%) was within the historical control range shown below (0-1.92%, rounded to 2 in the legend).

Year & Study	No. of Animals	No. of renal carcinomas
81E	52	0
82A	104	0
82C	52	0
82D	88	0
82E	52	0
82F	52	0
83A	52	0
82B	104	1
83B	52	1

The historical control data indicated that renal carcinomas had occurred in the range of 0 to 2 percent in the animals. However in 7 out of the 9 studies tumors occurred in 0 percent of the controls. In addition, no renal adenomas were reported in these historical data.

Other Effects

Other effects observed included body weight changes, increased liver weights, and kidney lesions. These included:

significantly decreased body weight gains in males at 700 and 4900 ppm (controls, 17.6g; 700 ppm, 8.9g; 4900 ppm, 12.7g)

Liver weights were increased in males at weeks 26 ($p<0.05$), 52 ($p<0.05$), and 104(not sig.); in females only at week 104 ($p<0.05$);

Gross pathology revealed only effects on the kidneys, namely cortical scarring in 4900 ppm males at weeks 26 and 52 and "pale kidneys" in 3/12 4900 ppm males at week 52;

Non-neoplastic lesions included dose dependent dilated/basophilic renal tubules in treated males and females, with

increased severity at the high dose; and centrilobular liver cell enlargement in 4900 ppm males at 52 weeks.

The high dose tested caused pronounced toxicity in males and some clear toxic effects in females, i.e. kidney lesions. Thus, the dose levels used in the study were judged to be adequate for assessing carcinogenicity.

Table 4. Ethofenprox - Male Mice Renal Cortical Tumor Rates[+] and Cochran-Armitage Trend Test and Fisher's Exact Test Results

	Dose(ppm)				
Tumor	0	30	100	700	4900
Renal Cortical Adenoma	0/64 (0)	0/59 (0)	0/62 (0)	0/63 (0)	2[a]/58 (3)
p=	0.002**	1.000	1.000	1.000	0.224
Carcinoma	0/64 (0)	0/59 (0)	0/62 (0)	1[b]/63 (2)	1/58 (2)
p=	0.095	1.000	1.000	0.496	0.475
Combined Tumors	0/64 (0)	0/59 (0)	0/62 (0)	1/63 (2)	3/58 (5)
p=	0.002**	1.000	1.000	0.496	0.104

[+] Number of tumor bearing animals/ Number of animals at risk (excluding those that died before 52 weeks).

( ) percent

a first adenoma observed at week 95.
b first carcinoma observed at week 98.

Note: Significance of trend denoted at Control.
Significance of pair-wise comparison with control denoted at Dose level.

If * then $p<.05$ and if ** then $p<.01$.

E. Additional Toxicity Data

1. Reproduction and Developmental Toxicity

A rat reproduction study showed increased liver weights in pups at weaning whose mothers received 700ppm; the NOEL was 100ppm.

A rat teratology study showed a non-specific increase in malformations and visceral anomalies, as well as salivation in the mothers, at 5000 mg/kg/day, with a NOEL of 250 mg/kg.

2. Chronic Dog Study

A chronic dog feeding study had a NOEL of 32 mg/kg, with a LEL of 350 mg/kg where organ weight increases, liver enzyme changes, and liver histopathology were seen, although these were reported as reversing 8 weeks after exposure.

3. Metabolism

Metabolism studies in rats and dogs showed that roughly 90% of excretion was in the feces 5 days after a dose of 30 mg/kg; 90% of that was excreted in 24 hours. 3.5-4 % of the dose was still present in the carcass after 5 days. The material was sequestered in fat as the intact molecule and was found in the milk of lactating pups. Roughly 10-25% (30-180 mg/kg) in rats and up to 50% in dogs (30 mg/kg) was found unchanged in the feces, suggesting limited absorption from the G.I. tract. Metabolism was considered to be chiefly by microsomal enzymes and to consist of hydroxylation of the ethoxyethyl ester and/or the terminal phenyl ring, followed by glucuronide/sulphate conjugation.

4. Mutagenicity

There were a variety of acceptable mutagenicity studies, including 2 negative Salmonella assays, a negative micronucleus assay, 2 negative human lymphocyte clastogenicity studies; and negative studies for DNA damage/repair and unscheduled DNA synthesis.

5. Structure Activity Relationships

While the registrant considered Ethofenprox a pyrethroid, it differs in structure in that it lacks a carbonyl group.

Fenvalerate, a pyrethroid somewhat related to ethofenprox, has been tested in rats at doses up to 250 ppm and in mice at doses up to 1250 ppm and reported not to be carcinogenic. However, in a single dose 2 year rat study, 1000 ppm in the diet caused spindle cell sarcoma in males. Fenvalerate also has been reported to cause cytogenetic effects in mouse bone marrow, but cytogenetic studies

available on ethofenprox are negative.

It should be noted that ethofenprox contains a dibenzyl ether moiety. Dibenzyl ether has been associated with carcinogenicity. However, available metabolism data on ethofenprox in rats and dogs indicate that the molecule remains intact and is not split at the ether linkages.

F. Weight of Evidence Considerations

The Committee considered the following facts regarding the toxicity of Ethofenprox to be important in weighing the evidence of its carcinogenic potential.

Ethofenprox, when administered in the diet to Sprague-Dawley rats at levels of 0, 30, 100, 700, and 4900 ppm was associated with: an increase for females in thyroid follicular cell adenomas at 4900 ppm and a significant positive trend in this tumor type for both sexes; in both sexes an increase in thyroid follicular cell adenomas and carcinomas combined in the 4900 ppm group and significant positive trends for these combined tumors.

In the rats, there were effects on liver weight and histopathology of the liver. Further, there were increased thyroid weights in males and some scattered evidence of decreased T3 levels (females only at week 25), and histopathology (females only).

Historical control data on the Sprague-Dawley rat combined thyroid adenomas and carcinomas indicated that the observed incidence in the present study was outside of the control range for both males and females.

Ethofenprox, when administered in the diet to CD-1 mice at levels of 0, 30, 100, 700, and 4900 ppm was associated with: a significant dose related trend in renal cortical adenomas alone and combined carcinomas and adenomas in male mice. There were no compound related increases in any tumors in females.

Kidney tumors were found only in male mice where severe kidney lesions were present. In addition, there was significant mortality in the mice.

Historical control data on renal carcinomas in CD-1 mice indicated that the observed incidence in this study was within the historical control range.

Both studies were considered to have used high enough dose levels to adequately assess the carcinogenic potential of Ethofenprox.

A variety of mutagenicity studies on gene mutation,

chromosomal aberrations, and DNA synthesis and repair were negative.

No good analogues were found on ethofenprox and data on Fenvalerate were only weakly positive and not similar to Ethofenprox. Analogy to the carcinogenicity of the dibenzyl ether moiety was limited by the metabolism data that indicated that this moiety would not be cleaved from the parent ethofenprox molecule.

G. Classification of Oncogenic Potential

Criteria contained in the EPA Guidelines [FR51: 33992-34003, 1986] for classifying carcinogens were considered.

The Peer Review Committee concluded that the evidence for carcinogenicity could best be classified as

Group C Possible Human Carcinogen.

This conclusion was based on: toxicologically significant increases in combined thyroid adenomas/carcinomas in male and female rats; and the fact that their incidence was outside the historical control range.

The Peer Review Committee also concluded that the kidney tumors in mice were not treatment related because the increase was not statistically significant by pairwise comparison to controls, because the incidence of carcinomas was within the historical control range, and because there was both significant kidney damage in mice with tumors and significant mortality in the high dose group.

The Committee further recommended that a quantitative risk assessment be performed on the thyroid combined adenoma/carcinoma data set for the same reasons these tumors were seen as significant, statistically significant pairwise increases at the high dose in both sexes, significant positive trends, incidences outside the historical control range, as well as the fact that the available evidence showed a greater and more widespread incidence of thyroid tumors than of systematic thyroid or liver dysfunction. While some scientists have argued that changes in liver function may affect thyroid physiology, and changes in thyroid function may lead to thyroid hyperplasia and perhaps neoplasias, the incidence and evidence of changes in thyroid and liver non-neoplastic endpoints was less than in the incidence of tumors, i.e. only at some time points and in one sex. Thus, these non-neoplastic effects did not correlate well with tumors.

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Chemical:	**Benzene, 1-((2-(4-ethoxyphenyl)-2-methyl**
PC Code:	**128965**
HED File Code	**21200 PEER REVIEW**
Memo Date:	~~**06/15/2004**~~ 05/24/00
File ID:	~~**00000000**~~ 000 5064 TXR
Accession Number:	**412-04-0243**

HED Records Reference Center
07/23/2004